LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

JAMES R. PHELPS
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ROGER C. THIES
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JOHN A. GILBERT, JR.
JOHN R. FLEDER
MARC H. SHAPIRO

ROBERT T. ANGAROLA
(1945-1996)

700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

MARY KATE WHALEN
OF COUNSEL

JENNIFER B. DAVIS
FRANCES K. WU
DAVID B. CLISSOLD
CASSANDRA A. SOLTIS
JOSEPHINE M. TORRENTE
MICHELLE L. BUTLER
PATRICIA A.A. VANSTORY
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DARA S. KATCHER*
KURT R. KARST*

*NOT ADMITTED IN DC

DIRECT DIAL (202) 737-4280

May 9, 2002

Dockets Management Branch
(HFA-09305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 02N-0101, International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs ... Buprenorphine, 67 Fed. Reg. 17074 (Apr. 9, 2002)

Dear Sirs:

On behalf of Purdue Pharma L.P., ("Purdue"), Hyman, Phelps & McNamara PC, provides the following comments in response to the Federal Register notice at:

DEPARTMENT OF HEALTH AND HUMAN SERVICES, Food and Drug Administration

[Docket No. 02N–0101], International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Amfepramone (diethylpropion); Amineptine; Buprenorphine; Delta–9–tetrahydrocannabinol (dronabinol); Tramadol.

67 Fed. Reg. 17074 (Apr. 9, 2002). We wish to comment specifically on the questionnaire with respect to buprenorphine.

02N-0101
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2603 MAIN STREET
SUITE 760
IRVINE, CALIFORNIA 92614
(949) 553-7400
FAX: (949) 553-7433

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX: (919) 313-4751

I. Summary

The World Health Organization ("WHO") is conducting a critical review to determine whether the control of buprenorphine should be changed from the 1971 Convention on Psychotropic Substances ("Psychotropic Convention") to the 1961 Single Convention on Narcotic Drugs ("Single Convention"). WHO supports the United Nations Drug Control Program by providing a scientific and medical analysis on appropriate use and misuse or abuse of drugs. Countries participate in this effort by providing WHO with information concerning domestic use and misuse or abuse of drugs. However, the WHO questionnaire on buprenorphine is deficient in that it does not encourage collection of information that will contribute to a thorough evidence-based analysis on the use and potential abuse of buprenorphine.

In addition, there is no evidence that any further control is necessary, given the known scientific and medical information on buprenorphine. Such action would have significant negative consequences for patients who would benefit from buprenorphine in the United States. For example, the Drug Addiction Treatment Act of 2000 ("DATA") was enacted to allow a much needed expansion of the treatment of drug addiction in this country, that is, permitting drugs controlled under schedules III, IV or V of the United States Controlled Substances Act ("CSA") that are approved for narcotic addiction treatment to be used in office-based practice by trained and certified physicians. The

proposal to change the international control status of buprenorphine will jeopardize the ability of buprenorphine to be used under the DATA, if such action requires rescheduling to schedule II of the CSA, as we believe that it would. Consequently, physicians would not be able to use buprenorphine in office-based treatment as contemplated by the DATA.

We have had an opportunity to review the recent eight-factor analysis on buprenorphine[1] submitted by the Department of Health and Human Services to the Drug Enforcement Administration ("DEA") in relation to DEA's proposed rescheduling of buprenorphine to schedule III of the CSA.[2] This document consisted of a review by the Food and Drug Administration. ("FDA Analysis"). We are concerned that FDA's Analysis (which may reasonably be considered to represent the current DHHS view on buprenorphine) is not an adequate basis on which to answer the WHO questionnaire. There are two reasons for this, either of which is sufficient on its own to render the FDA Analysis inadequate as a basis for the US response to the WHO questionnaire.

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1 Recommendation to Reschedule Buprenorphine From Schedule V to Schedule III of the CSA. Forwarded From HHS to DEA via letter from Arthur J Lawrence, PhD, Assistant Surgeon General, to Mr. Asa Hutchinson, Administrator DEA dated December 4, 2001 [hereinafter "FDA Analysis"].

2 67 Fed. Reg. 13114 (Mar. 21, 2002). This notice was based on the FDA 8 factor analysis as well as an analysis by DEA that relied extensively on the analysis by FDA.

First, the FDA Analysis relies heavily on foreign data. While it is not unreasonable for the US to consider such data for domestic purposes, the US is not asked to provide data regarding abuse of buprenorphine in foreign countries in response to the questionnaire, and it should refrain from doing so. Second, the FDA Analysis is flawed. The FDA does not accurately describe the data reviewed and its conclusions that buprenorphine has a higher potential for abuse than drugs in schedule IV and that buprenorphine abuse may lead to low or moderate physical dependence or to high psychological dependence are unsubstantiated.

We request that the U.S. government response that is made consist entirely of objective unbiased information concerning current domestic medical use and abuse of buprenorphine.

Therefore, in responding to this questionnaire the United States:

1. Should refrain from providing an ad hoc response that would not accurately reflect the current data on this useful drug substance.
2. Should provide data that only addresses domestic medical use and abuse of buprenorphine.
3. Should inform WHO of the negative impact that any change in the international control status of buprenorphine would have on the medical use of buprenorphine in the United States.
4. Should inform WHO that its medical and scientific analysis of buprenorphine and the current DEA proposed rule to reschedule buprenorphine to schedule III of the US Controlled Substances Act do not support the international rescheduling of buprenorphine and that the US is opposed to such action.

The following is a discussion of Purdue's concerns in regard to the US response to the WHO Questionnaire and FDA's current analysis of buprenorphine. We also have provided an analysis of the data that we believe accurately reflect the current situation concerning the extent of legitimate medical use and low actual and potential abuse of buprenorphine in the US. We believe this information should form the basis for responding to the WHO questionnaire.

II. The WHO Questionnaire is Inadequate for Conducting a Scientific and Medical Review of Buprenorphine Use and Abuse.

Purdue recognizes that the UN scheduling process under the conventions has a profound effect upon health policy in the United States. Decisions made in the UN process will affect the controls that will be placed on medicines here, and thus the access of patients to needed health care. Pain patients, for example, frequently depend upon scheduled medicines. Proper scheduling decisions are important to these patients and others, and should be made on solid, correct medical and scientific information. The WHO questionnaire, which is the subject of this Federal Register notice, is not an appropriate means to achieve sound decisions.

Purdue objects to the WHO questionnaire's use as a tool for the making of health policy. The questionnaire is sent to every nation that has signed the international conventions, and is intended to be used by WHO's expert committee to evaluate the current

worldwide state of use/abuse of subject substances. The questionnaire is totally inadequate for this purpose.

The document propounds a few unsophisticated questions calculated to elicit anecdotal responses. Neither Purdue nor representatives of our government know the identities or capabilities of the personnel answering the questionnaires for other countries. Possibly because of the inadequacy of the questionnaire, the number of non-responses to it is notoriously high. WHO does not permit affected parties to see the results obtained from the questionnaire, though some parts of the "data" may be revealed at the election of the WHO's secretariat.

The WHO is considering whether to transfer control of buprenorphine from the Psychotropic Convention to the Single Convention. The reason for this is not evident. WHO's expert committee considered whether to put buprenorphine and other partial agonists under one convention or the other as recently as 1988. The record shows there was full consideration given and a proper rationale developed for putting buprenorphine and the other drugs under the Psychotropic Convention. Absent some compelling reason for doing so, and none is apparent, it is folly to disrupt the practice of medicine by switching control of buprenorphine from one convention to the other.

The WHO questionnaire provides the only formal mechanism by which the United States can participate in WHO's medical/scientific deliberations. Addressing this gaping

imperfection in the UN scheduling process should be a high priority for our government. But, given the reality that the questionnaire will be used for this cycle of drug scheduling decisions, it is necessary that our government provide a balanced presentation of data that will permit the WHO's experts to make decisions based on sound data, and not anecdotes.

In the United States, for example, the DATA was made law in order to provide treatment for addicts in the offices of specially trained physicians. If these treatment programs proceed, they will bring relief in areas of our country untouched by the current, clinic-limited ones. A change in the international control status of buprenorphine would prevent use of the drug by physicians in office treatment if such action requires rescheduling to schedule II of the CSA, as we believe that it would. Congress specifically intended that buprenorphine be available for use in addiction treatment under DATA. It is bad public health policy for the US to relinquish control of domestic health care decisions in the absence of a compelling need.

How the switch to Single Convention coverage might affect other countries, including especially those in the Third World, is uncertain. It is known that all over the world the more severe the restrictions upon medicines, the more difficult it is for them to be used in medical practice. The phenomenon of 'opiophobia' is described in WHO literature and medical literature. Converting buprenorphine to a drug with severe regulation will certainly limit its use by physicians, and this will occur at a time when WHO and all the

world recognizes the need to do just the opposite – to encourage the use of analgesics for those in need.

The data show conclusively that there is no demonstrated need for the kind of restrictions that would be required if buprenorphine were placed under the Single Convention. There is no evidence of the need for any change in the international control of buprenorphine. We are unaware of any information that would nullify the findings of the WHO Expert Committee on Drug Dependence (ECDD) in 1988 that buprenorphine is appropriately controlled in schedule III of the Psychotropic Convention.

III. The FDA Analysis is Inadequate as a Basis for a Response to WHO Regarding Buprenorphine.

The FDA Analysis fails to provide a rational and balanced explanation as to why buprenorphine should be rescheduled from schedule V to schedule III of the Controlled Substances Act (CSA). Thus, its usefulness in responding to the WHO questionnaire is similarly deficient. Many of the studies cited by FDA as supporting their position, in fact, do not support the conclusions reached by FDA. Results are taken out of context, arc not discussed in sufficient detail and are presented without proper scientific and medical context. Moreover, as discussed below, the FDA Analysis (and the DEA proposed rule that is based on this analysis) places emphasis on outdated information and fails to fully evaluate other, critical issues. As a result, the FDA Analysis and all documents derived from it fail to meet the current standard of objectivity in rulemaking. Therefore none of

these documents should serve as the basis for the US response to WHO regarding buprenorphine.

A. The FDA Analysis does not meet current standards of objectivity in rulemaking.

Congress recently enacted the Information Quality Act, section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001. The Office of Management and Budget ("OMB") subsequently issued "Guidelines for Ensuring and Maximizing the Quantity, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, 67 Fed. Reg. 369 (Jan. 3, 2002), to implement the Act. The Act requires each agency, including FDA, to adopt standards for ensuring the quality and accuracy of information the agency disseminates, and to provide procedures for challenging the agency's information.

Under the law and guidelines, each federal agency must adopt a basic standard of quality as a performance goal and take appropriate steps to incorporate quality into their information dissemination practices. OMB Guidance § III(1), 67 Fed. Reg. at 376. Each agency must ensure that the data disseminated meets the "utility" standard, that is, the usefulness of the information to the intended user and "objectivity" standard, whether the information in terms of both presentation and substance is accurate, reliable and unbiased. Id. at 376-77.

The discussion below provides several examples of areas in which we feel the FDA Analysis does not meet these standards.

B. FDA cites the purported increase in the rate of abuse of butorphanol following the marketing of butorphanol nasal spray to assert that abuse of buprenorphine will increase when Subutex® and Suboxone® are approved for use in this country.

FDA speculates that the potential abuse of new dosage forms of buprenorphine will be similar to abuse of butorphanol (which was not controlled under the CSA when first marketed in the US as a parenteral formulation) following the marketing of a nasal spray formulation of that drug.

The FDA Analysis indicates that the introduction of a nasal spray dosage form did lead to an increase in reports of abuse of butorphanol, at a time when the use of parenteral butorphanol was reported to be stable.[3] The number of reports of abuse or dependence involving parenteral butorphanol remained low and stable (less than 5 per year before and after marketing of the nasal spray formulation) and the proportion of reports involving parenteral butorphanol (6/165 for the period mid 1992 to 1994) is the same as the percentage of the retail market for butorphanol represented by that formulation (4%). As Bristol Myers Squibb commented in response to the DEA recommendation to schedule

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[3] FDA Analysis at 6. "From 1992 to 1994, there was a 600 percent increase in prescription sales for butorphanol. In contrast, there was no change in the prescribing of Stadol Injectacble from 1989 to 1994."

butorphanol, "the abuse potential of butorphanol nasal spray is low as evidenced by the low number of adverse reaction reports received by the company per number of prescriptions."[4] Butorphanol has never been reported in the published Drug Abuse Warning Network ("DAWN") reports except for 1996 when it had 239 weighted mentions, the lowest number of any opioid reported in table 2.06a for that year.[5]

Spontaneous Reports Related to Abuse and Dependence of Butorphanol Submitted to FDA, 1978 to 1994 and Prescribing as % of market

	Butorphanol Parenteral	Butorphanol Nasal Spray
Reports Submitted 1978-mid 1992	70 (4.8 reports/y)	--
% of Reports Submitted 1978-mid 1992	100%	0%
Reports Submitted mid 1992-1994	6 (2.4 reports/yr)	159 (63.6 reports/yr)
% of Reports Submitted mid 1992-1994	**4%**	**96%**
% of Total Rx 1978-mid 1992	100	0
% of Total Rx mid 1992-1994	15%	85%
% of retail market for butorphanol 1994	**4%**	**96%**

Source: FDA Analysis at 6-7, December 4, 2001.

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4 62 Fed. Reg. 51370 (Oct. 1, 1997).

5 DRUG ABUSE WARNING NETWORK DETAILED EMERGENCY DEPARTMENT (ED) TABLES 1996. Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Department of Health and Human Services Table 2.06a. Butorphanol has not subsequently appeared in this table. (Drugs with fewer than 200 weighted mentions are excluded).

Although the FDA Analysis claims that butorphanol nasal spray increased the rate of abuse of butorphanol, [6] the rate of reports of butorphanol abuse rose only in proportion to the medical use of butorphanol and overall abuse of butorphanol has been low. Thus, despite its initial unscheduled status and about 1.5 million prescriptions per year for butorphanol nasal spray in 1996, the actual abuse of the partial agonist butorphanol was and remains low.

This is consistent with the observation of Joranson[7] who has recently examined the relationship between the legitimate medical use and abuse of opioids with data from the DAWN system and has not found an increase in the rate of abuse of many full mu agonist opioids despite substantial increases in the legitimate medical use of these agents in recent years. Using data from DAWN and the Automation of Reports and Consolidated Order System ("ARCOS") this study demonstrated that increases in the use of schedule II analgesics did not result in increases in the abuse of these medications. DAWN, a measure of the consequences associated with drug abuse, is sponsored by the Substance Abuse and Mental Health Services Administration ("SAMHSA"). ARCOS provides data on the

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6 FDA Analysis at 7: "In 1997, as a result of the increased rates of abuse and dependence, butorphanol was subsequently placed in Schedule IV of the CSA."

7 Joranson DE. Ryan KM. Gilson AM. Dahl JL. Trends in medical use and abuse of opioid analgesics. JAMA. 283(13):1710-4, 2000 Apr 5.

distribution of narcotics in total grams and grams per 100,000 population and is sponsored by the Drug Enforcement Administration.

Five opioid analgesics, morphine, fentanyl, oxycodone, hydromorphone and merperidine were included in Joranson's analysis. The DAWN mentions for these drugs decreased from 7,476 in 1990 to 5,494 in 1996. During this time medical utilization of these five drugs decreased slightly from 9,159,261 grams in 1990 to 9,040,926 grams in 1996. However this decrease was likely the result of decreases in the use of meperidine. If meperidine is removed from the analysis the DAWN mentions decreased from 6,141 to 4,688, while medical use increased from 3,936,124 grams to 5,660,486 grams. This 44 percent increase in medical use did not result in the increased abuse of these products as measured through the consequences of drug abuse in DAWN.

Thus, the FDA position that the rate of abuse of opioids increases with their legitimate medical use is unfounded. Such speculation cannot be provided in response to WHO's request for information on current medical use and abuse of buprenorphine in the United States. As the FDA has acknowledged, there is negligible diversion of buprenorphine in the United States.[8] Providing such unfounded speculation to WHO in lieu

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[8] FDA Analysis at 6.

of data will undermine any chance that the critical review of buprenorphine will be based on scientific and medical data.

C. The FDA Analysis relies extensively on foreign data. The United States has not been requested to provide this information to the WHO.

FDA's reliance on foreign data in support of its recommendation to reschedule buprenorphine in the United States makes this document inappropriate for use in any way for a response to the WHO questionnaire. Under the WHO system, it is the responsibility of individual governments to provide data concerning the use of buprenorphine in their own countries. It is inappropriate for the United States to respond to the WHO questionnaire by attempting to report or interpret data from any other country. We are confident that France and other countries will fulfill their responsibility to the WHO by providing their own data.

D. The foreign data cited on abuse of analgesic dosage forms of buprenorphine is not current and does not reflect the actual low level of abuse of buprenorphine following its placement under the Psychotropic Convention in 1989.

When foreign data are presented by FDA they are not presented in their proper scientific context, thereby giving a misleading impression of the current low level of actual abuse of buprenorphine. For example, among reports describing the situation in Scotland,[9]

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[9] FDA Analysis at 13 and 14.

Sakol, [10] Morrison, [11] Gray, [12] Hammersly,[13] and Gruer[14] all report observations that were made either partly or entirely prior to the international control of buprenorphine in 1989. Indeed, FDA acknowledges that these reports date from the late 1980's but does not note even the possibility that they might not be relevant to the current situation in which buprenorphine is now controlled internationally. The same is true of most of the reports cited by FDA. In fact, of the 43 reports of abuse of analgesic dosage forms of buprenorphine that we identified from the indexed medical literature, 22 involve observations that were made entirely prior to the international control of buprenorphine in 1989 and an additional 8 reports contain some observations from before 1989.

Furthermore, the WHO Expert Committee on Drug Dependence ("ECDD") considered such early reports of buprenorphine abuse when making the following finding,

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10 Sakol MS, Stark C, Sykes R. Buprenorphine and temazepam abuse by drug takers in Glasgow—an increase [letter]. Brit J Addict 1989;84:439–41.

11 Morrison V. Psychoactive substance use and related behaviours of 135 regular illicit drug users in Scotland. Drug Alcohol Depend 1989;23:95–101.

12 Gray RF, Ferry A, Jauhar P. Emergence of buprenorphine dependence [letter]. Brit J Addict 1989;84:1373–4.

13 Hammersley R, Lavelle T, Forsyth A. Buprenorphine and temazepam—abuse. Br J Addict 1990;85:301–3.

14 Gruer L, Cameron J, Elliott L. Building a city wide service for exchanging needles and syringes. BMJ 1993 May 22;306(6889):1394-7.

> The committee rated the likelihood of abuse of buprenorphine as moderate and the therapeutic usefulness of the drug as moderate to high. The degree of seriousness of the public health and social problems associated with this drug was found not to be great in terms of the numbers of individuals involved and the impact of abuse on their wellbeing. [15]

We note that the actual finding of the ECDD regarding abuse of buprenorphine is at variance with its characterization by FDA as "widespread abuse by heroin addicts and by individuals who were not already abusing heroin or other opiates."[16]

When FDA does cite data concerning the abuse of buprenorphine that dates from after the international control of buprenorphine, that is, 1989, it is presented incompletely, and without proper scientific context. For example, in a study of adolescents aged 13 to 16 FDA reports that Coggans[17] found that 1.4 percent of youth had tried buprenorphine. Drugs which had been tried more frequently than buprenorphine included cannabis (15.3%), magic mushrooms (7.3%), temazepam (6.5%), LSD (5.7%), amphetamines (3.8%), DF118 (dihydrocodeine, 2.3%) and barbiturates (1.7%). The use of these drugs

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15 WHO Expert Committee On Drug Dependence 25th Report. Technical Report Series 775. World Health Organization, Geneva, 1989. Section 4.2.6, page 23.

16 FDA Analysis at 15.

17 Coggans N, Shewan D, Henderson M, Davies JB. The impact of school-based drug education. Br J Addict. 1991 Sep;86(9):1099-109.

provides a relevant comparison, suggesting a low abuse potential for buprenorphine, but is not described by FDA.

The study by Shewan[18] is the only study cited by FDA to support the statement "examination of frequency of use data in Glasgow revealed that some opioid abusers used buprenorphine frequently. Buprenorphine was used as a heroin substitute at times when heroin was either unavailable, of low quality, or relatively too costly."[19] In fact, the study by these authors reported interviews with 74 opioid users who had never been in treatment or served a custodial sentence. Virtually all those interviewed had used tobacco, alcohol, cannabis, LSD, amphetamine, MDMA, psilocybin and benzodiazepines. The majority used heroin (72/74), opium (57/74), and dihydrocodeine (50/74). Buprenorphine was sixth on the list of seven opioids. Only 23 of 74 had tried buprenorphine and it was the least preferred of all the opiates. The modal frequency of use of buprenorphine in the last 2 years was 1 and it was reported to be the first opiate used by only 6 of the 74 interviewees. Using a scale where 1 was "highly enjoyable" and 5 was "did not like at all,' heroin was rated 1.2 and buprenorphine 3.6. It cannot be said based on these data that the subjects in this study abused buprenorphine frequently or that they preferred it to other drugs.

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[18] Shewan D, Dalgarno P, Marshall A, Lowe E, Campbell M, Nicholson S, Reith G, Mclafferty V, Thomson K, Patterns of Heroin Use among a non-treatment sample in Glascow (Scotland), Addiction Research, 1998; 6(3) 215-234.

Other than the observations of Coggans and Shewan, there are no recent reports of abuse of buprenorphine in Scotland. There are also no recent reports from New Zealand where the most recent reports[20] both contain data from 1992 (even though one of these was published in 1997). The only reports from Spain that include data from after 1989 include those of Segui, [21] and San.[22] None of these reports appear to contain data obtained after 1990, and none of them was published after 1993. The interpretation of these data is that

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19 FDA Analysis at 17.

20 Dore GM, Hargreaves G, Niven BE, Cape GS. Dependent opioid users assessed for methadone treatment in Otago: patterns of drug use. N Z Med J 1997;110:162–5. Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. Drug Alcohol Depend 1993;33:81–6.

21 Note that the following reports represent triplicate publication of the same data: Segui J, Cascio A, Aragon C, Llovet JM, Soler JM, Salvador L. Subgroups of drug abuse patients who consume buprenorphine . An Med Interna 1991;8:18–22. Segui J, Cascio A, Aragon J, Llovet M, Soler M, Salvador L. Prevalence of buprenorphine consumption in a sample of outpatient drug abusers [in Spanish]. Rev Clin Esp 1991;189:14–7. Segui J, Cascio A, Aragon C, Llovet JM, Soler JM, Salvador L. Buprenorphine use, a bad prognostic indicator in drug dependence [in Spanish]. Actas Luso Esp Neurol Psiquiatr Cienc Afines 1992;20:17–22.

22 San L, Torrens M, Castillo C, Porta M, de la Torre R. Consumption of buprenorphine and other drugs among heroin addicts under ambulatory treatment: results from cross-sectional studies in 1988 and 1990. Addiction 1993;88:1341–9. San L, Cami J, Fernandez T, Olle JM, Peri JM, Torrens M. Assessment and management of opioid withdrawal symptoms in buprenorphine-dependent subjects. Br J Addict. 1992 Jan;87(1):55-62. The date of the publication notwithstanding, study report notes that some of the data was presented in 1990.

abuse of buprenorphine subsided within a few years following its international control in 1989.

This leaves India and some neighboring countries as the only places currently reporting abuse of buprenorphine. As FDA acknowledges, "the drug is sold often without valid prescriptions..."[23] but FDA does not acknowledge that this situation is in violation of India's existing treaty obligations under the Psychotropic Convention and that this uncontrolled access to buprenorphine simply does not apply to the United States. Many of the papers cited by FDA (Basu, Chowdhury, and Singh) still represent data from before international control of buprenorphine.[24]

Many authors, including some of those cited by FDA (Basu, Bedi, Chowdhury, Singh and Kumar—but see Kumar 2000)[25] describe the fact that buprenorphine is accepted

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23 FDA Analysis at 14.

24 Basu D, Varma VK, Malhotra AK. Buprenorphine dependence: a new addiction in India. Disabil Impair 1990;3:142–6. Chowdhury AN, Chowdhury S. Buprenorphine abuse: report from India. Br J Addict 1990;85:1349–50. Singh RA, Mattoo SK, Malhotra A, Varma VK. Cases of buprenorphine abuse in India. Acta Psychiatr Scand 1992;86:46–8.

25 In addition to Basu, Chowdhury and Singh, see: Bedi NS. Ray R. Jain R. Dhar NK. Abuse liability of buprenorphine--a study among experienced drug users. Indian Journal of Physiology & Pharmacology. 42(1):95-100, 1998 January Kumar MS, Mudaliar S, Thyagarajan SP, Kumar S, Selvanayagam A, Daniels D. Rapid assessment and response to injecting drug use in Madras, South India. Int J Drug Policy 2000;11:83–98.

for addiction treatment in India and prescribed by physicians there. Singh reported 18 cases of buprenorphine dependence among patients at the author's "de-addiction" clinic. However, it must be noted that these were identified from among 107 cases of opiate dependence seen at this clinic in the same period (a fact not disclosed by FDA, but which indicates a low level of abuse despite buprenorphine's use as an addiction treatment). Three of these were concurrent heroin users, 2 of whom reported less euphoria than heroin than before abusing buprenorphine. (It must be acknowledged that such reports are consistent with the pharmacology of buprenorphine as a partial mu opioid agonist with high receptor affinity.) The reasons given for starting buprenorphine were nonavailability of heroin (10 cases), to decrease heroin intake (14 cases) and low cost (3 cases). Surely such reasons for abusing buprenorphine—together with the low rates of abuse actually reported—do not suggest that buprenorphine is a preferred substitute for heroin. A similarly low rate of buprenorphine abuse by Indian addicts attending a "de-addiction" clinic is reported by Chowdhury (highest rate reported was 30/285 cases in 1989).

Singh notes:

> Almost all cases graduated to buprenorphine from heroin and 14 of 17 shifted either due to nonavailability of heroin or to decrease the heroin consumption, confirming earlier reports that buprenorphine is abused not as the preferred drug but as an alternative to heroin. The preference of the buprenorphine diazepam cocktail abuser for the cocktail over buprenorphine alone confirms the earlier subjective patient reports that

> buprenorphine has a low euphoriant effect and that cocktail with temazepam or cyclizinc enhances this effect.

Even Bedi characterizes the abuse potential of buprenorphine as moderate. Furthermore, the prevalence of buprenorphine abuse in their clinical population is low: "Between 12 and 14% of patients registered in our OPD (De-addiction center) abuse buprenorphine intravenously either alone or in combination with diazepam or promethazine (unpublished data), though abuse of buprenorphine tablet is rare."

The low prevalence rates noted above are all clearly described in the reports by these authors (18/107 (17%) by Singh, 30/285 (11%) by Chowdhury, 12-14% by Bedi). This information is clearly relevant to the abuse liability of buprenorphine. The low frequency of abuse of buprenorphine given its accessibility and the corresponding scarcity of heroin, clearly indicate the low abuse potential of buprenorphine. Yet these and other quantitative data described above are not reported by FDA in its analysis. [26]

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[26] It may be claimed that the study of Kumar indicates a higher prevalence of buprenorphine injection. However, this study recruited subjects using a 'snowballing' technique. As such, the study provides useful information by demonstrating the lesser consequences of buprenorphine vs. heroin injecting, but it cannot estimate the relative size of these 2 populations.

FDA has thus failed to accurately describe data relating to the abuse of analgesic dosage forms of buprenorphine in countries outside the United States. Such inaccurate information cannot be used as the basis for a United States response to WHO in this matter.

E. The introduction of Subutex in France has led to a dramatic decline in heroin overdose deaths in that country which FDA does not consider.

FDA places great significance on the abuse of buprenorphine in France, but does not consider all the data. Abuse of analgesic dosage forms of buprenorphine has only been reported from France following the testing of Subutex as a treatment for addiction in 1987.[27] The only source from which the relative prevalence of abuse can be estimated[28] reports the frequency of buprenorphine abuse (by urinalysis) in a series of 50 addicts hospitalized in Marseilles June to October 1992. Substances identified were: heroin: 40/50; Benzodiazepines: 36/50; Cannabis 10/50; Buprenorphine: 9/50; Cocaine 3/50; Amphetamines 0/50. One of the 9 cases was an attempt to substitute buprenorphine therapeutically. These data suggest a low rate of abuse of buprenorphine, particularly considering that triplicate prescription was not required until the end of 1992 and that

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27 Auriacombe M, Franques P, Daulouede JP, Tignol J. The French Experience: results from extensive delimited research studies and nationwide sample surveys. Research and Clinical Forums,1999, 21(3) 9-15.

28 Arditti J, Bourdon JH, Jean P, Landi H, Nasset D, Jouglard J, Thirion X. Buprenorphine abuse in a series of 50 drug addicts hospitalized at a drug dependence evaluation hospital in Marseille. Therapie 1992;47:561–2.

clinical investigation of Subutex in France had begun about 5 years earlier such that buprenorphine would have been well known to French addicts by that time. In its discussion of this study with respect to abuse of buprenorphine in France, FDA says only that it shows that abuse and diversion of buprenorphine in France were identified "soon after approval."[29] The actual proportion of specimens that were positive for buprenorphine is not reported by FDA nor is the proportion of specimens positive for other drugs.

In its analysis, FDA relies heavily on the French experience when Subutex was introduced in that country for the treatment of addiction in 1996. For example, FDA states "since the approval of the high-dose sublingual formulation in France in 1996, over 100 reports of death linked to abuse of the new formulation have been received."[30] FDA further reports "because of continuing reports of abuse and diversion, on September 20, 1999, restrictions on dispensing of buprenorphine were tightened to a 7 day supply at one time per prescription."[31] Such statements provide a false impression that the only consequence

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29 FDA Analysis at 12.

30 FDA Analysis at 1. Similar statements appear at 5, 15 to 16.

31 FDA Analysis at 13. To our knowledge, based on correspondence with Marc Auriacombe, a French physician who has been extensively involved with investigation and use of Subutex in France, this statement is incorrect. When Subutex was introduced in 1996 the dispensing period for a Subutex prescription was 28 days unless a shorter period was indicated by the physician on the prescription. The regulatory change in 1999 made the dispensing period for Subutex 7 days, unless a longer period (up to 28 days) was indicated by the physician.

of the use of Subutex in France has been abuse of buprenorphine, respiratory depression, and additional drug-related deaths.

In fact, the French have documented a dramatic, positive impact of the availability of Subutex (and methadone) treatment on addicts in that country. In 1994, 505 heroin overdose deaths were reported by the French Ministry of the Interior. Following the introduction of methadone substitution treatment in specialized drug treatment centers in France in 1995 and the introduction of Subutex into French General Practice in 1996, heroin overdose deaths fell to fewer than 100 per year by 1998.[32] This information is included in many reports from France—including the report by Kintz[33] describing the 117 overdose deaths that are referred to several times in the FDA Analysis. Kintz himself acknowledges that substitution with buprenorphine has been "successful." Instead of reporting this information, FDA cites Kintz' assessment that he considered the number of

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Publications that have appeared since that time (including that of Kintz which was published in 2001 and contains data through mid 2000) continue to indicate, contrary to the impression given by FDA, that 28 day dispensing is still permitted. FDA does not provide a citation in support of this statement.

32 Drug use and drug trafficking in France: 1998 annual statistics. Paris, France: Ministry of the Interior, Director's Office of the National Police, Central Directorate of the Judicial Police, Central Office Against Illicit Drug Trafficking; March 1999. p. 8.

33 The published version of this case series is Kintz, P, Deaths involving buprenorphine: A compendium of French cases. Forensic Science International 2001 121:65-69.

deaths reported in his study to be an underestimation of the problem. While this may be true, Kintz' statement is speculative because his report provides no information on the number of forensically documented fatal heroin overdoses for comparison. Therefore, the only valid conclusions that can be drawn from these data concern the toxicology of buprenorphine associated deaths.

In fact, the series of 137 buprenorphine-associated deaths that have been published (the first 20 cases reported by Tracqui[34] were followed by 117 cases reported by Kintz) covering the period from 1996 through mid 2000 (an average of about 3 deaths per month) show the safety of buprenorphine in overdose. Toxicological analysis of these cases revealed that 115 of the 117 deaths involved multiple substances in addition to buprenorphine—an average of 3.3 drugs per fatality (most commonly including benzodiazepines). In fact, in only 2 of these 137 deaths (1.5%) was buprenorphine the only drug identified. Such a situation is simply not seen with full mu opioid agonists such as methadone.[35] The safety of buprenorphine compared to methadone in overdose has been

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34 Tracqui has reported the series of 20 fatalities at least 3 times. The most extensive discussion is in: Tracqui A, Tournoud C, Flesch F, Kopferschmitt J, Kintz P, Deveaux M, Ghysel MH, Marquet P, Pepin G, Petit G, Jaeger A, Ludes B. Acute poisoning during substitution therapy based on high-dosage buprenorphine: 29 clinical cases-20 fatal cases. Presse Med 1998;27:557–61.

35 See, for example, Cooper GA, Seymour A, Cassidy MT, Oliver JS. A study of methadone in fatalities in the Strathclyde Region, 1991-1996. Med Sci Law. 1999

confirmed by other data from France[36] showing that the rate of deaths attributable to methadone (a full mu opioid agonist) in France is substantially higher than that attributable to buprenorphine, despite the substantially greater restrictions placed on the use of methadone compared to Subutex in France. FDA does not describe the tremendous public health benefit of Subutex that these data represent even though the necessary information was available for its consideration.[37]

The deaths reported by Kintz and Tracqui occurred over a period that extended from early 1996 through mid 2000. The FDA presents these data in juxtaposition to an estimated number of addicts in treatment of 50,000 during the first 3 years of Subutex used in France.[38] The amount of buprenorphine imported into France is similarly reported to have

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Jul;39(3):233-42. About 9% of the fatalities in this study were positive for methadone alone.

36 Auriacombe M., Franques P., Tignol J., Deaths Attributable to Methadone vs. Buprenrophine in France, JAMA 2001 Jan. 3; 285 (1):45.

37 The FDA has been provided with extensive information relating to the abuse liability of buprenorphine. This information included inter alia the report of the French Ministry of the Interior and the report by Ariacombe discussing "Deaths attributable to methadone and buprenorphine in France."

38 FDA Analysis at 16.

risen from 5kg in 1994 to 159kg in 1998 and to have coincided with "an increase in buprenorphine abuse and reports of death."[39]

There are several problems with the FDA presentation of these data. First, Auriacombe[40] reports approximately 129,000 patient years of exposure during the first 3 years of Subutex use in France (1996-1998), with approximately 55,000 patient years of treatment in 1998 alone. More current data on the use of buprenorphine in France are available and show a continuing increase in the medical use of buprenorphine during the time period covered by the reports of Kintz and Tracqui. For example, the International Narcotics Control Board ("INCB") reported an annual domestic medical and scientific requirement for buprenorphine in France at 250 kg in 2000.[41] This translates into about 80,000 patient years of Subutex treatment at an average dose of 8mg per day.

In this case, the FDA presentation of buprenorphine data reinforces the misinterpretation noted above that the legitimate medical use of Subutex has only had negative consequences for France. The reporting of buprenorphine data from a different

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39 FDA Analysis at 6. Once again FDA is reinforcing the misconception that the only effect of buprenorphine has been drug abuse and death.

40 See footnote 36.

41 Psychotropic Substances, Statistics for 1999, Assessments of Medical and Scientific Requirements for Substances in Schedule II, III and IV. United Nations, 2001.

period of time than was reported by Tracqui and Kintz creates the false impression that the buprenorphine associated deaths reported from France occurred over a shorter period of time and resulted in a higher rate per patient year of treatment than is actually the case. This will substantially overstate the toxicity of buprenorphine in relation to its legitimate medical use and is not acceptable. Finally, presenting these data without presenting data on the decline in heroin related deaths implies that there is no therapeutic benefit of buprenorphine. This could not be further from the truth.

E. FDA does not describe the differences between the use of Subutex in France and those allowable under the Drug Addiction Treatment Act of 2000; Nor does FDA explain why abuse of Subutex has not been reported from 11 countries in which the product has been approved since at least 1999.

It is important that the U.S. government provide the WHO with all relevant information on the use of buprenorphine in the U.S. including the entire medical and regulatory framework. Because the applicable international conventions obligate the United States to conform with international controls, a discussion of the DATA is crucial to the US position on the proposed international rescheduling of buprenorphine. The DATA created the opportunity for office-based treatment of addiction and will significantly improve access to treatment for narcotic addiction. Currently, a sizeable population of addicts have gone untreated. Congress recognized that the DATA would make buprenorphine available for treatment and noted that "buprenorphine is not addictive like

methadone so that the likelihood of diversion is small."[42] Congress also noted that then Secretary Shalala had sent a letter of support for the DATA commenting that "buprenorphine and buprenorphine/naloxone products are expected to have low diversion potential."[43]

In passing the DATA, Congress specifically acknowledged that buprenorphine had a low potential for abuse and would provide a useful substitution therapy for schedule II drugs. The Act provides for waivers to authorize qualifying physicians to treat a limited number of patients in an office setting to expand the availability of drug treatment to all areas of the country. Certification under the DATA requires inter alia, that the physician have "the capacity to refer the patients for appropriate counseling and other appropriate ancillary services." In addition, the government shall issue a treatment improvement protocol containing best practice guidelines to assist practitioners in treatment. These provisions create appropriate safeguards to reduce the potential for abuse of buprenorphine or other drugs used pursuant to the Act.

Given the DATA, it is reasonable to assume that the US experience will be different than that in other countries. In France, buprenorphine may be prescribed by any general

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42 146 Cong. Rec. S 9094, S 9112 (Sept. 22, 2000).

43 Id.

practitioner. Special training is not required. While this approach may provide addicts with maximum access to buprenorphine, it certainly creates opportunities for abuse that will be sharply reduced in the US. In fact, SAMHSA's request for approval of information gathering activities related to the DATA anticipates few physicians applying for a waiver under the Act.[44]

In light of the clear differences between France and the US with respect to the use of substitution treatment, FDA fails to explain adequately why it believes that France "is an appropriate comparator for the United States, because the drug is marketed there both for the treatment of pain and opiate dependence" [45] and why the provisions of the DATA will not be adequate to control abuse of buprenorphine in this country. FDA's own analysis of this matter[46] shows that Subutex has been approved in at least 11 countries besides France since 1999 (Argentina, Austria, Denmark, Finland, Iceland, Italy, Luxembourg (1998),

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44 See 67 Fed. Reg. 19443. SAMHSA estimates the burden of the form at 1200 initial applications for purposes of the Paperwork Reduction Act. This translates to a maximum number of 36,000 addicts under treatment with buprenorphine via a waiver through the Drug Addiction Treatment Act, which allows a maximum of 30 treated addicts per registrant. This level of buprenorphine use outside the context of traditional drug treatment programs is modest and does not suggest that the emergence of significant buprenorphine diversion and abuse is inevitable or even likely.

45 FDA Analysis at 6.

46 FDA Analysis at 3-4.

Norway, Sweden, Switzerland and the UK.) Reports of abuse of Subutex in France were published within 1 to 2 years of its approval in that country.[47] In light of the rapidity with which reports of abuse of buprenorphine emerged from France following the marketing of Subutex there in 1996, FDA's assertion that "[d]ata on the marketing, usage, or abuse are unavailable on the high-dose sublingual buprenorphine tablets which were not approved for treatment of opiate dependence in the United Kingdom until late 1999"[48] is simply untenable.

F. Contrary to the implication of FDA, neither craving nor drug seeking behavior is part of the diagnostic criteria for opioid withdrawal nor is craving a criterion for opioid dependence.

Although as discussed previously, the WHO questionnaire is not designed to solicit scientific and medical information, the US must take the opportunity to provide the most relevant and accurate information on the use and potential for abuse of buprenorphine and other drugs, including information relating to the proper diagnosis and treatment of addictive disorders. FDA relies on the definitions of substance abuse and dependence contained in the American Psychiatric Association's Diagnostic and Statistical Manual of

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47 Decocq G, Fremaux D, Smail A, Compagnon M, Andréjak M. Local complications after intravenous injection of dissolved tablets of buprenorphine [letter]. Presse Med 1997;26:1433. Gourarier L, Lowenstein W, Gisselbrecht M, Chauveau JM, Haas C, Durand H. Withdrawal syndrome in two drug addicts after intravenous injection of buprenorphine. Presse Med 1996;25:1239–40.

48 FDA Analysis at 13.

Mental Disorders, Fourth Edition, Text Revision, 2000 (DSM IV TR™)[49] in making its case that abuse of buprenorphine may cause low or moderate physical dependence or high psychological dependence. Establishing this level of physical or psychic dependence is critical to the determination that buprenorphine should be controlled in schedule III of the CSA. However, in its analysis, FDA implies[50] that the withdrawal syndrome that results from discontinuation of opioid administration[51] leads to the lack of control over use of an opioid or other drug that characterizes addiction or substance dependence.[52] In fact, the diagnosis of substance dependence according to DSM-IV-TR requires the presence of any 3 (or more) of the following: tolerance, a substance specific withdrawal syndrome, **or** any of 5 indicators of a patient's lack of control over drug use. Neither tolerance nor a withdrawal syndrome are necessary or sufficient for the diagnosis of dependence.

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49 See FDA Analysis at 18.

50 See for example FDA Analysis at 18. In describing the opioid withdrawal syndrome FDA states, "The first symptoms are subjective and consist of complaints of anxiety, restlessness, and muscle pains often in the back and legs, accompanied by a wish to obtain opioids (craving) and drug-seeking behavior." See also FDA Analysis at 20: "Drug craving has been reported after discontinuing use of buprenorphine, which in some patients resulted in the need to resume use of heroin."

51 DSM-IV-TR, page 273.

52 DSM-IV-TR, pages 197-198.

In addition "craving" (the subjective desire to use a drug) is not part of the diagnosis of either withdrawal syndrome or substance dependence (addiction) although it is likely to be present in persons with substance dependence.[53] Moreover, the development of a withdrawal syndrome (for example in newborns of mothers treated with buprenorphine or in the studies of buprenorphine withdrawal cited by FDA) documents only the capacity of buprenorphine to produce physical dependence. It does not address the capacity of a drug to produce psychological dependence.

In addition to failing to accurately define the diagnostic criteria for the disorders of opioid withdrawal and opioid dependence according to its chosen source, FDA seriously mischaracterizes the studies of spontaneous buprenorphine withdrawal that it cites in support of the contention that withdrawal from buprenorphine may lead to drug seeking behavior. These studies are the reports of Seow[54], Kosten,[55] San[56], and Fudala[57] cited in the

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53 DSM-IV-TR, page 192.

54 Seow SS, Quigley AJ, Ilett KF, Dusci LJ, Swensen G, Harrison-Stewart A, Rappeport L. Buprenorphine: a new maintenance opiate? Med. J. Aust., 1986 Apr. 14;144(8):407-11.

55 Kosten TR, Kleber HD. Buprenorphine detoxification from opioid dependence: a pilot study. Life Sci. 1988;42(6):635-41.

56 San L, Cami J, Fernandez T, Olle JM, Peri JM, Torrens M. Assessment and management of opioid withdrawal symptoms in buprenorphine-dependent subjects. Br J Addict. 1992 Jan;87(1):55-62.

FDA Analysis at page 19. FDA describes the study by Seow by saying that the authors studied:

> heroin dependent outpatients receiving 2 or 4 mg sublingual buprenorphine. After 21 days of controlled buprenorphine administration, the subjects were allowed to abruptly withdraw from buprenorphine. The subjects responded unfavorably to cessation of buprenorphine due to an increase in withdrawal symptoms. Subjects requested treatment of symptoms or transfer to a methadone program. These effects were reversed after readministration of buprenorphine.

FDA describes the last 3 studies by saying "abrupt discontinuation of buprenorphine produced a withdrawal syndrome characterized as moderately severe: effects peaked at 3 to 5 days, with a gradual lessening in intensity 8 to 10 days after the last dose." In this instance, FDA provides descriptions of data that do not accurately represent what the authors have done and what they have reported. It is particularly important that there is no evidence of psychological dependence on buprenorphine and no evidence of buprenorphine seeking behavior reported in any of the studies cited. Considered as a whole the studies only demonstrate a minimal level of physical dependence on buprenorphine.

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[57] Fudala PJ, Jaffe JH, Dax EM, Johnson RE. Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. Clin Pharmacol Ther. 1990 Apr;47(4):525-34.

For example, Seow studied a group of 32 patients who were receiving buprenorphine from their general practitioners for treatment of heroin dependence. The prior doses of buprenorphine were not reported, but they had been treated for an average of 7.4±3.3 months. Patients were assigned to treatment with either 2 or 4 mg of sublingual buprenorphine per day for 2 weeks. All subjects were treated with placebo during week 3 and then treated with buprenorphine again at their previous dose for weeks 4 and 5. Benzodiazepines, clonidine and dextropropoxyphene were used to treat withdrawal symptoms.

In total, 14 patients received additional treatment. Twelve (12) patients were treated during the placebo week. All of them received dextropropoxyphene. Nine (9) of them received clonidine and temazepam concurrently. These drugs were issued daily for anywhere from 1 to 10 days (average 3 days). The authors note that higher doses of buprenorphine had been used in previous studies. They report that the doses used in this study were insufficient, as indicated by the fact that opioid positive urines had increased to approximately 50% in both groups by week 5. Despite inadequate dosing, 21 patients completed the study. Dropouts were 2 during weeks 1 and 2, 4 during week 3 (placebo) and 3 during week 4. When the circumstances of the study are fully considered, the proportion of subjects remaining in the trial who requested medication for withdrawal symptoms during the placebo week (12 out of 28) is low.

Requesting treatment with methadone is entirely appropriate behavior and certainly is not craving nor is it drug seeking behavior. While it may be the case that the addicts who were abusing opioids during this study had craving this is not reported by the authors, and there is no indication that the opioids they were abusing included buprenorphine. The addicts certainly had access to buprenorphine if they chose to abuse it (since they were on buprenorphine prior to entering the study). The results of this study do not suggest that buprenorphine may cause a level of physical or psychological dependence similar to other drugs in schedule III of the CSA.

Kosten studied 2, 4 and 8 mg of sublingual buprenorphine daily for 30 days in 16 opioid addicted patients. A total of 10 patients received 2 mg buprenorphine daily while 4 patients received 4 mg and 2 patients received 8mg. Half of the patients came from methadone treatment at doses of 25mg per day and half were street addicts. Study retention and abstinence during the study were described as "excellent." A total of 13 patients completed buprenorphine treatment and 26 of 122 urine samples were positive during the trial. Among subjects completing the trial, the subjects taking 8 mg of buprenorphine reported a "substantial increase in withdrawal symptoms" after abrupt discontinuation of buprenorphine and "refused to take naltrexone for fear of further withdrawal." However, in the 2 and 4 mg groups "minimal withdrawal was observed following discontinuation [of buprenorphine] and low dose naltrexone did not precipitate withdrawal." The authors state

"[i]f methadone maintenance were abruptly stopped at 20 mg daily, patients would report substantial withdrawal. Furthermore, if naltrexone were given to these patients, it would precipitate withdrawal within minutes." The authors go on to note "the overall rate of starting naltrexone (7/13=54%) was substantially higher than we obtained with outpatient clonidine (6/24=25%) or methadone tapering over 30 days (6/23=26%)." In this instance, FDA has mischaracterized the withdrawal reported by this study by failing to fully describe that patients abruptly discontinuing buprenorphine at daily doses of 2 and 4 mg per day experienced "minimal" withdrawal and were reported to be more likely to transition to naltrexone than patients detoxified in other ways. It is unlikely that addicts with high psychological dependence on opioids would be so willing to transition to naltrexone treatment as were the participants in this study.

San describes a placebo-controlled study of physical dependence among 22 Spanish heroin addicts who had spontaneously switched from heroin to sublingual or intravenous buprenorphine. Patients were an average of 29 years old, had started heroin consumption at an average age of 21 and had been using buprenorphine for an average of 8 months with a mean daily dose of 2 mg. About 80% of subjects were using buprenorphine intravenously. Subjects were recruited from 10 outpatient facilities in Barcelona and assigned either to methadone or placebo for detoxification. Doses of methadone were based on the history of buprenorphine use, with maximum possible methadone doses ranging from 15 to 60 mg.

Based on the algorithm used, 10 of the patients in the methadone group received detoxification starting at 15mg and 1 patient started at 45mg. In the placebo group, 8 patients met criteria for detoxification with a 15mg starting dose and 3 met criteria for a 30 mg starting dose. Eight of the 11 patients on placebo met criteria for change in treatment to methadone. None of the patients on methadone met criteria for adjustment of their tapering regimen. Ten of the 11 patients on methadone and 8 of the 11 patients on placebo completed the 13 day detoxification (including 3 who continued to receive placebo).

The fact that no patients in the methadone group (and even 3 patients in the placebo group) required modification of this dosing regimen indicates that a starting dose of methadone less than the 15 mg per day used in this study would be adequate to substitute for buprenorphine. This dose of methadone is substantially less than that typically used in methadone maintenance treatment of heroin addicts in which doses of methadone between 60 and 100mg per day are clearly more effective than 20 mg per day.[58] The fact that even lower doses of methadone are effective in detoxification from buprenorphine and that even lower doses of methadone than those tested in this study would likely have been adequate

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[58] Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med 2000;343(18):1290-1297.

strongly support the fact that buprenorphine produces a low level of physical dependence and little psychological dependence.

Fudala compared the effects of buprenorphine 8mg per day given daily (9 subjects) or every other day (10 subjects) to heroin dependent male volunteers. Beginning on study day 37 subjects were switched to placebo. Two subjects on each buprenorphine regimen left the study after the switch to buprenorphine placebo. Four subjects on each regimen did not require therapeutic intervention for withdrawal after the termination of buprenorphine. Among these subjects, withdrawal as measured by the opioid withdrawal adjective rating scale peaked at 3 to 5 days and diminished over 8 to 10 days following discontinuation of buprenorphine. In comparing their results to those of Jasinski from 1978, the authors note that the withdrawal syndrome peaked earlier and seemed to be mild to moderate as opposed to minimal. They cited several factors (including differences in dosing, measurements, study duration and study populations) that may have contributed to the differences observed. Among subjects that were medicated for withdrawal symptoms, 6 subjects received a total of 2 or fewer doses of temazepam, propoxyphene or clonidine.

Although FDA is clearly aware that the subjects in these studies were heroin addicts (or addicts in treatment), the agency fails to acknowledge the implications of this fact and fails to interpret the results accordingly. In an addicted population, drug abuse (relapse) is a sign of therapeutic failure; it is not an indication that the drugs that are used or abused in

this population may cause high psychological dependence as implied by FDA. Rather, the capacity of buprenorphine to produce psychological dependence must be based on data concerning actual abuse of pharmacologically related drugs. As discussed above, the rate of abuse of buprenorphine and the other partial opioid agonists is low and adequately controlled by the measures required under the Psychotropic Convention. This can neither be said of the full mu agonists controlled for therapeutic use under the single convention, nor can it be said of heroin.

In fact it is the capacity of these latter drugs to produce a pattern of sustained abuse in susceptible individuals despite high levels of legal control and the great risks associated with that abuse that marks full mu agonists as capable of producing high psychological dependence. Partial opioid agonists, including buprenorphine, can sustain little abuse among susceptible individuals even when they are available without significant legal control. Considering the susceptibility of the populations in the studies cited by FDA to physical and psychological dependence on opioids, the prevalence of withdrawal from buprenorphine is low and its severity is minimal. Moreover, none of these studies documents psychological dependence on buprenorphine, a fact that is truly remarkable considering the susceptibility of the populations studied.

In this instance, FDA has failed to be scientifically rigorous in its application of the diagnostic standards of DSM IV-TR. It has also failed to accurately describe data from

studies that it claims support its conclusion that buprenorphine may produce high psychological dependence. The assertion that buprenorphine abstinence produces a withdrawal syndrome that is more than minimal in severity or that includes craving and drug seeking behavior is speculative and has no place in any rulemaking, either domestic or international.

IV. The US Response to the WHO Questionnaire on Buprenorphine Should be Confined to Specific Factual Domestic Data.

Neither the FDA Analysis nor any documents derived from it (including the DEA analysis of buprenorphine and the DEA Federal Register notice proposing to reschedule buprenorphine to schedule III of the US CSA) accurately reflect the existing data and therefore should be excluded in any response to the WHO questionnaire. Rather than speculating in response to WHO concerning the abuse of buprenorphine in this country, FDA should report actual data. The response to WHO should note that:

1. Buprenorphine is currently being used off label for the treatment of heroin addicts in the United States.[59] The proportion of such use appears to be substantial.[60] It is

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[59] Henney, Clarification on Buprenorphine, JAMA 2000 284(17) 2178. It is essential that the response should in no way indicate that such off label use is not a legitimate medical use of buprenorphine.

[60] According to the National Disease and Therapeutic Index from IMS Health, 75% of all U.S. buprenorphine prescriptions for the year 2000 were for addictions treatment.

also being actively studied for this use by the National Institute on Drug Abuse ("NIDA"), such that the INCB assessment for buprenorphine in the United States has increased from 0.3kg in 1995 to 2.4 kg in 1999. The estimated assessment for 2002 of 30.2 kg in the U.S. appears to reflect an amount of buprenorphine for use under the DATA.

2. Information on the public health or social problems possibly associated with drugs are obtained from DAWN. DAWN is a measure of the consequences of drug use as measured through hospital emergency rooms. DAWN is a national probability survey of hospitals and emergency rooms conducted by the SAMHSA. Estimates are generated for the approximately 4,800 hospital emergency rooms in the United States.

Buprenorphine has never appeared in DAWN, this includes the period prior to the introduction of the probability sample when any drug with at least 10 mentions was included as well as the period following the implementation of the probability sample when all drugs with at least 200 estimated mentions were included in the published data.

A recent report which includes trend data from 1994 to 2000 and which includes all mentions (without the 200 mentions limit) demonstrates the virtual absence of any consequences or social harm emanating from the abuse of buprenorphine. The table below includes the DAWN mentions for a number of drugs including drugs currently in CSA schedules III, IV, & V. The data in the table includes reported suicide attempts and gestures that should normally be excluded from the data when drug abuse and dependence

are being considered, since there is no implication, in suicide attempts, of loss of control over use that would normally be indicative of substance dependence according to DSM IV TR. This is not drug abuse and should not be considered as evidence of public health concerns or social harm for purposes of domestic or international drug control. The impact of including suicide attempts and gestures in DAWN is exemplified by heroin/morphine where only 5% of the mentions are suicide-related compared to alprazolam and propoxyphene where suicide attempts represent 65% and 56% of the mentions respectively. Even if the suicide attempts and gestures are removed from the data, these drugs have substantially more mentions than the partial/mixed agonists. It is clear from these data that the abuse of partial/mixed agonists including buprenorphine cause little or no social harm.

Estimated Emergency Department Mentions for Selected Drugs 1994-2000 Drug Abuse Warning Network[61]							
	1994	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**
Heroin/morphine (C-1/II)	63,158	69,556	72,980	70,712	75,688	82,192	94,804
Alprazolam (C-IV)	17,168	17,082	16,655	17,468	17,833	20,484	22,105
Acetaminophen/propoxyphene (C-IV)	5,216	5,224	4,822	5,337	4,714	4,816	4,891
Acetaminophen/Hydrocodone (C-III)	8,168	8,362	9,845	10,667	11,686	13,043	17,538
Buprenorphine (C-V)	2	2	1	...**	0	...	11
Butorphanol (C-V)	35	...	239	...	19	...	...
Nalbuphine (Rx)	13	13	10	14	...	33	...
All Pentazocine NX (C-IV)	289	153	196	202	329	262	224

*Suicide Attempts and Gestures are included in the table although they do not represent drug abuse
**Estimate with RSE >50% has been suppressed

61 Office of Applied Studies; Emergency Department Trends from DAWN, Preliminary Estimates, January- June 2001 with Revised Estimates 1994-2000.

3. There is insignificant trafficking of buprenorphine during this time. Data from the US National Forensic Laboratory Information System ("NFLIS") for the period 1998 through 2000 includes data on 93,552 analyzed drug exhibits for heroin and pharmaceutical opioids (including morphine, hydrocodone, oxycodone, hydromorphone, fentanyl, pentazocine buprenorphine and the unscheduled opioid tramadol). Eighty percent of the mentions were for heroin; 20% were for other full mu agonist opioids. The partial mu opioid agonists, buprenorphine and pentazocine, together accounted for 0.1% of the drugs mentioned in the system and buprenorphine accounted for 0.02% of mentions of the opioids reviewed in the system. A similar low level of trafficking is apparent from DEA's STRIDE database (see table).

I. Distribution of seizures from STRIDE for Hydrocodone, Buprenorphine and Pentazocine 1985-2000

	Buprenorphine (C V)		Pentazocine (C IV)		Hydrocodone (C III)	
Year	# Seizures	# 0.3 mg Doses	# Seizures	#50 mg Doses	# Seizures	#5 mg Doses
1985	0	-	25	5999	18	4659.2
1986	0	-	15	886.7	11	293.9
1987	0	-	12	3749	16	114.2
1988	0	-	9	2424.2	20	2,116
1989	0	-	7	166	41	1253.1
1990	0	-	7	71	44	1,260
1991	0	-	3	56.4	45	55,274.8
1992	0	-	2	12	55	4,824
1993	0	-	14	429.2	121	5,897.4
1994	0	-	2	16	91	4,844,7
1995	0	-	1	24	96	11,345.3
1996	11	10	4	45.7	131	7,462.6
1997	3	0*	0		173	133,585.4
1998	3	0	0		76	67,046
1999	4	657	21	453.9	203	18,871
2000	7	30	0		226	68,288.7

*0 means trace amount or not quantified

4. The US is obligated to make changes to the Federal CSA to be consistent with changes to the Single Convention. Therefore, the rescheduling of buprenorphine from its current position in schedule III of the Psychotropic Convention to the Single Convention as proposed we believe would require the domestic rescheduling of buprenorphine to schedule II of the CSA.

The rescheduling of buprenorphine to schedule II under the CSA will make Subutex and Suboxone ineligible for use under the terms of the Drug Addiction Treatment Act. The use of Subutex and Suboxone would then be restricted to methadone clinics. These clinics do not operate in 9 of the 50 states. The clinics that do exist are located mainly in urban areas, leaving rural areas unserved even in states that allow methadone treatment. Such restriction would be unwarranted given the safety of buprenorphine and clearly contrary to the clear intent of Congress in passing this law. Thus any international rescheduling of buprenorphine will have a serious negative impact on the heath and well being of drug addicts who will be unable to benefit from this important new treatment International rescheduling will also impose unnecessary restrictions on the medical use and availability of analgesic dosage forms of buprenorphine including Temgesic®, Buprenex®, and transdermal formulations that are currently under development.

V. The United States Must Inform WHO that it Opposes International Rescheduling of Buprenorphine as Part of its Response to the WHO Questionnaire on Buprenorphine.

It is contrary to sound health policy for the US to wait until the Commission on Narcotic Drugs meeting in 2003 to state that US law and our medical and scientific analysis require that we oppose international rescheduling of buprenorphine. Any delay in informing WHO of our position will jeopardize the use of these products under DATA. The Federal Register Notice concerning the international scheduling of buprenorphine states:

> DHHS will not now make any recommendations to WHO regarding whether any of these drugs should be subjected to international controls. Instead, DHHS will defer such consideration until WHO has made official recommendations to the Commission on Narcotic Drugs, which are expected to be made in late 2002. Any DHHS position regarding international control of these drugs will be preceded by another Federal Register notice soliciting public comments as required by section 201(d)(2)(B) of the CSA.

This position is unacceptable. The WHO questionnaire is the main, although flawed, vehicle to provide WHO with data for their scientific review by the ECDD. Once a scheduling recommendation is made by ECDD, it cannot be reopened on medical or scientific grounds by the CND. The deficiencies in the WHO questionnaire will only be compounded by the serious deficiencies in the current scientific and medical evaluation of

buprenorphine conducted by FDA. The DATA and the proposed rescheduling of buprenorphine from schedule V to schedule III of the CSA obligate the United States government to oppose the international rescheduling of buprenorphine. The United States must inform WHO that the data do not support any change in international control and of the serious negative impact of international rescheduling of buprenorphine on the medical use of Subutex and Suboxone in this country. Because this rescheduling is based on a medical and scientific analysis, it is appropriate to inform the WHO and the ECDD of our position in this matter immediately.

VI. Conclusion

For the foregoing reasons, we urge our government to take a strong position that buprenorphine should remain where it is, controlled under schedule III the Psychotropic Convention. This position is consistent with the U.S. government's position that buprenorphine should be controlled in schedule III of the CSA. We take strong exception to the statement that the United States will withhold making a recommendation until after WHO has forwarded its medical/scientific judgment to the Commission on Narcotic Drugs. There is no good reason for this reluctance to take a stand. Our government has access to the fullest body of data in the world, and the recommendation made by WHO will affect an important program just enacted by our Congress. If the United States does not take a position now, it will not be in a position to make effective interventions later in the process.

Therefore, we repeat that the United States should declare, now, its opposition to any change in international control of buprenorphine.

Sincerely,

James R. Phelps

cc: Purdue Pharma L.P.